Comments on the NTP inhalation studies of Alpha MethylStyrene (AMS)

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Critical Points

- NTP results support alpha-2-u-globulin nephropathy (α 2u-N) mediated mechanism for induction of kidney tumors in male rats.
- The incidence of hepatocellular adenomas and carcinomas in the chamber control was lower than the mean of the historical control in B6C1F1 female mouse inhalation studies.
  - This may account for the apparent statistically significant tumor increase observed in female mice.
- The Maximum Tolerated Dose (MTD) was exceeded in certain exposure groups of male and female mice which confounds the interpretation of the study results.

EPA's Criteria for Male Rat Kidney Carcinogens Operating through the α2u-Globulin-Mediated Mechanism

- Non-genotoxic chemical
- Increased number and size of hyaline droplets
- Accumulating protein is α2u-globulin
- An additional aspect of the pathological sequence of lesions associated with α2u-globulin nephropathy is present:
  - linear mineralization of papillary tubules

Kidney tumor induction after 2-year exposure to AMS is weak

AMS Single Section	AMS Step Section	Decalin Single Section
0/50 (0 ppm)	1/50 (0 ppm)	1/50 (0 ppm)
0/50 (100 ppm)	2/50 (100 ppm)	3/50 (25 ppm)
2/50 (300 ppm)	3/50 (300 ppm)	7/50 (50 ppm)
2/50 (1000 ppm)	7/50* (1000 ppm)	12/50* (100 ppm)
		6/20* (400 ppm)

* Significant increase in adenoma/carcinoma (combined)

Dose-responses for end-points characteristic of α2u-N are similar in AMS and Decalin 3-month exposures

symbol represents exposure concentration in which renal tumors were found to be significant

Findings may be confounded by the control incidence of liver tumors in Female mice

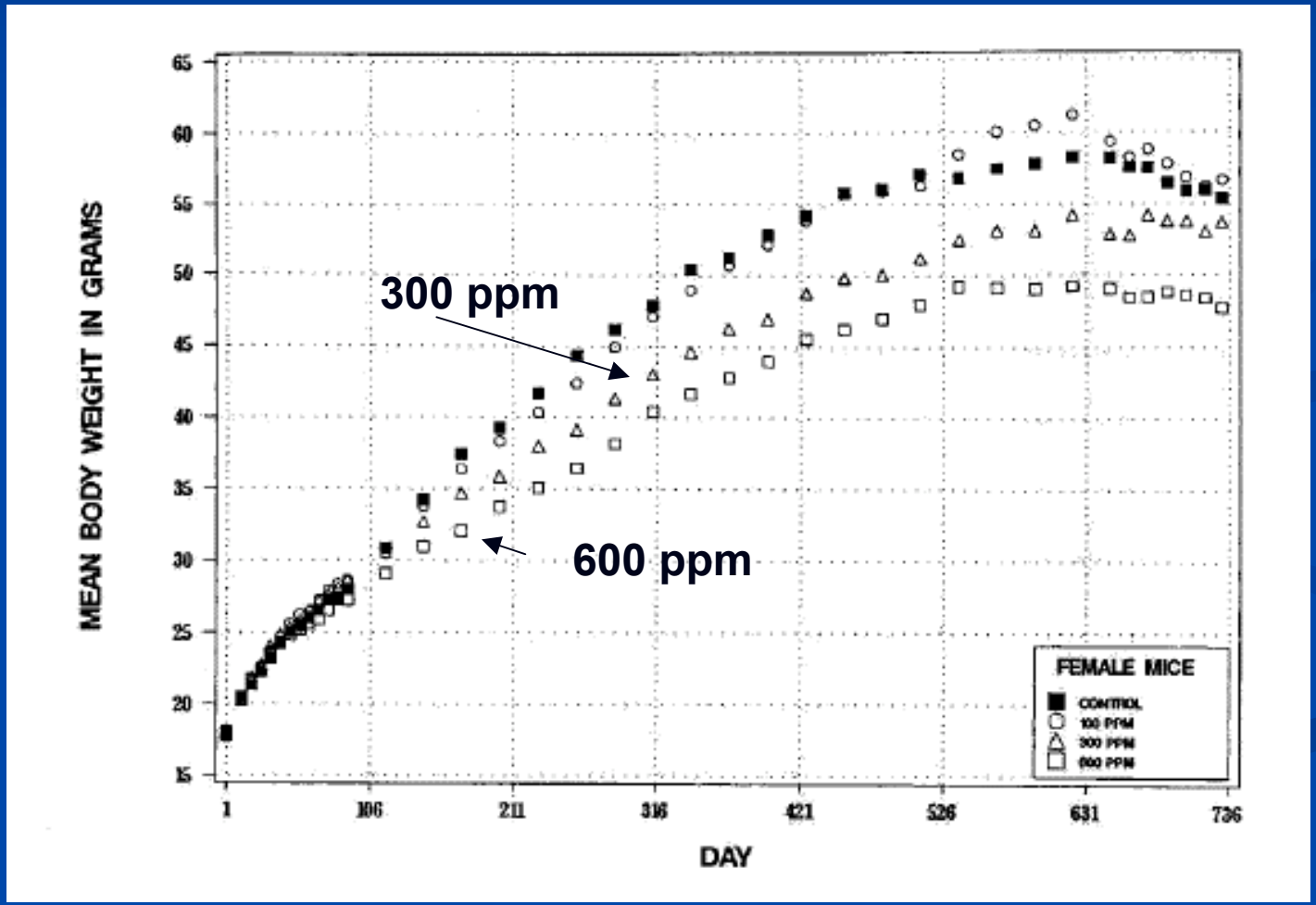
Incidences of Liver Lesions in Female Mice in the 2-Year Inhalation Study of AMS

	Historical Control	Chamber	100 ppm	300 ppm	600 ppm
Incidence of Hepatocellular Adenoma or Carcinoma	31.1%±6.8	Control 26%	52%	48%	66*%

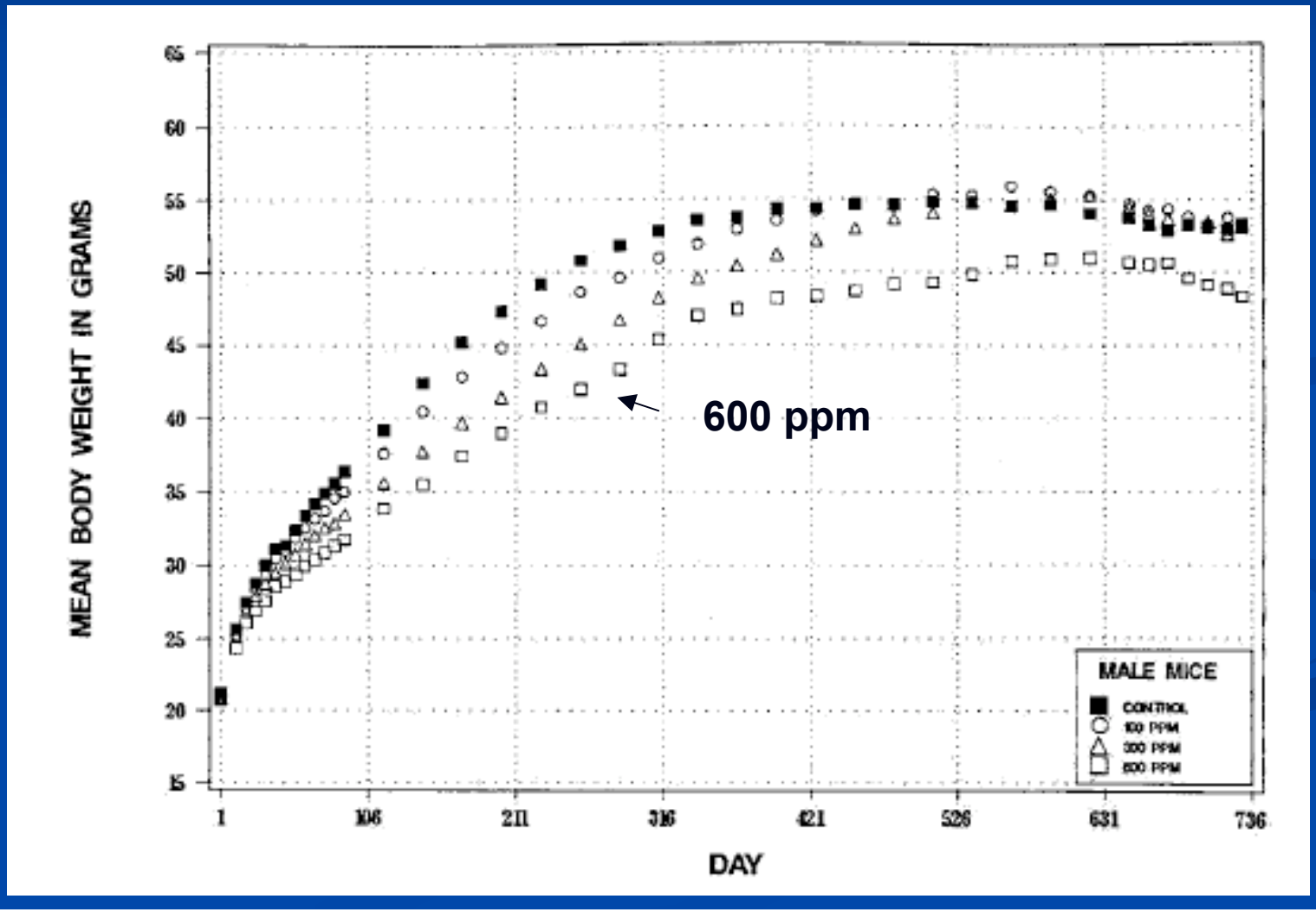
Evidence for exceeding NTP's MTD

- In the NTP, the MTD is defined as the highest dose that does not cause >10% decrease in body weight gain and survival relative to the controls during the study or a toxic lesion of a severity that would confound the study
- Body weights relative to controls of both male and female mice were significantly decreased starting at about 16 weeks.
  - The magnitude of the difference exceeded the MTD in the 600 ppm dose males and at 300 and 600 ppm dose females.
- This may confound mouse findings.

Evidence for exceeding NTP's MTD in female mice



Evidence for exceeding NTP's MTD in male mice



Conclusion

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